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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/601,444	01/04/2001	Esther H. Chang	2444-101	3962

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/601,444	Chang
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 6, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22 and 24-83* is/are pending in the application.

4a) Of the above, claim(s) *1-12, 29, 30, 39, and 51* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *13-22, 24-28, 31-38, 40-50, and 52-83* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 4, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 13, 31, 38, 40, 47-50, 52. 58, 63, 66, 67, 69 have been amended, claims 23 and 70 have been canceled, and claims 71-83 have been added by the amendment dated May 6, 2003.

Applicant's election with traverse of group II claims, *e.g.*, claims 13-28, 31-37, 40, 41-50, 63-70, and of species of a tumor cell targeting ligand, a therapeutic nucleic acid, a liposome mean diameter of about 30 to 75 nm, and a ratio of 0.1 to 50 nM liposomes per 1.0 ug nucleic acid, in the response filed April 26, 2001 is acknowledged. Applicant's election with traverse of a species of a therapeutic agent, which encodes a protein, in the response filed August 26, 2002 is also acknowledged.

Claims 1-12, 29, 30, 38, 39, 51, and 58-62 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Elected claims 13-22, 24-28, 31-38, 40-50, 52-69, and 71-83, directed to a liposomal complex of less than 100 nm comprising a cell targeting ligand, a liposome and a therapeutic agent, and methods of providing the therapeutic agent to a target cell, and a process specifically adapted for the manufacture of the products that are claimed in the elected claimed invention, are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-22, 24-28, 31-38, 40-50, 52-69, and 71-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1/ A liposomal vector for the systemic delivery of an anti-tumor or diagnostic agent to a target cell within a host animal, wherein the vector comprises an accentric structure based complex of a cell-targeting ligand, a cationic liposome comprising DOTAP/DOPE or DDAB/DOPE, and said agent, wherein the vector has a mean diameter of less than about 100 nm, and wherein the ligand is bound directly to the liposome which encapsulates said agent;

2/ A method of ameliorating a tumor in a mammal, the method comprising administering to a tumor bearing mammal the liposomal vector of 1/, wherein said agent is an anti-tumor agent, and whereby the tumor in the mammal is ameliorated.

does not reasonably provide enablement for any other claimed embodiment as broadly claimed in the presently pending claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The presently pending claims are not enabled for any cationic lipid/helper lipid/DNA complex other than DDAB/DOPE/plasmid DNA and DOTAP/DOPE/plasmid DNA.

While the specification provides sufficient guidance including working examples showing the

making of the complexes composed of DDAB/DOPE cationic liposome/cell targeting ligand/plasmid DNA or DOTAP/DOPE/ cell targeting ligand/plasmid DNA, wherein the entire complex has a mean diameter of 30-100nm (average 50 nm, page 77 of the specification), and wherein the liposome encapsulates the DNA, the issue is then would a skilled artisan be able to reasonably extrapolate from the guidance to the making and use of any other cationic lipid/ligand/DNA complex/therapeutic agent, which must be reduced in size to the required limitation of less than 100 nm, as a result of the only manufacturing process disclosed in the as-filed specification, wherein the process mainly employs step of mixing and incubating any targeting ligand with any cationic lipid, neutral or helper lipid, and any theapeutic agent, *e.g.,* hydrophobic proteins, hydrophilic proteins, hydrophilic drugs, hydrophobic drugs, small molecular weight drugs, antibodies, for a time period of 10-15 minutes.,

However, the state of the prior art with respect to the making of compact cationic liposomes/plasmid DNA, as exemplified by Lee *et al.,* Critial Reviews in Therapeutic Drug Carrier Systesm, 14, 2:173-206, 1997, states:

> Because uncondensed plasmid DNA has a hydrodynamic diameter in the same range as liposomes (100 –200 nm, depending on the number of base pairs and the topology of the molecule), it is difficult to produce compact vector particles without efficient DNA condensation. Cationic liposomes expecially those composed of monovalent cationic lipids, cannot condense DNA efficiently. Formation of spaghetti-like structures during liposome/DNA complexation is usually accompanied by the generation of vectors of relatively large size with a tendency to aggregate (page 187, last paragraph).

The essential feature of the average diameter of the liposomal complexes being below 100 nm or the accentric structure is disclosed for DOTAP/DOPE/ligand/plasmid DNA and DDAB/DOPE/ligand/plasmid

DNA, however, the as-filed specification does not provide sufficient guidance for a skilled artisan, without any undue experimentation, but only on the basis of applicant disclose, which relies only on general steps of mixing and incubating the liposomal components within some ratios parameters, to reasonably adjust the liposome/plasmid DNA dimensions in such narrow ranges (normal is 100 or more).

With respect to applicant's contemplation of claiming any method of gene therapy and/or the use of any liposomal carrier having the claimed diameter as a vector gene therapy, the state of the prior art with respect to non-viral gene therapy remains reasonably unpredictable at the time the invention was made.

More specifically, Lee *et al.* states:

> Because gene transfer efficiency is determined by a large number of factors, many of which are not well understood, it is difficult to predict the performance of a specific cationic liposome formulation based simply on the cationic lipid structure and/or the lipid composition. The gene transfer property of a vector is determined by 1) particle (DNA/lipid) size; 2) lipid composition; 3) lipid/DNA ratio; 4) formulation procedure; 5) DNA concentration; 6/ strength and tissue specificity of the promoter and enhancer elements; 7) for *in vitro* gene delivery, cell line, duration of transfection, cell confluency level, presence or absence of serum, etc; and 8? For *in vivo* delivery , route of adminstration (page 184);

More specifically as to applicant's intended use of the claimed vector for systemic and targeted gene therapy for treating any disease or disorder, Kao *et al.* (Cancer Gene Therapy, 3, 4:250-256, 1996) teaches:

> Targeting of cationic liposomes to specific cell surface epitopes appears to provide us with a means not only to achieve selective delivery of gene therapy to specific cells but also to increase the efficiency of transfection *in vitro.* However, with one or two notable exception, to date there are no

> successful examples of satisfactory transfection after systemic administration of liposomes, and no examples exist of successful transfections *in vivo* using targeted liposomal DNA systemically. Although we have achieved targeted delivery of liposomal anticancer drugs to tumors *in vivo*, using long-circulating sterically stabilized liposomes, cationic lipid-DNA complexes have short circulation half-lives. We expect that consider formulation development, directed at increasing the circulation times of the liposomal DNA, will be needed before targeted DNA delivery to cancer cells will be needed before targeted DNA delivery to cancer cells will be realized *in vivo* (page 255, column 2).

The specification also does not provide sufficient guidance and/or evidence so as to overcome the doubts expressed by the art of record. A simple inhibition of a tumor in a nude murine model wherein a particular formulation of DOTAP/DOPE/ligand/p53 expressing plasmid DNA or of DDAB/DOPE/ligand/p53 expressing plasmid does not appear to be correlated to any therapeutic effect by using any other therapeutic DNA, in cancer gene therapy in any cancer patient, let alone in any other gene therapy for treating any disease or disorder in any animal. Therefore, one skilled in the art then turns to the state of the prior art for guidance as to the state of the art of gene therapy of employing a cationic lipid/DNA complex. The state of the art of gene therapy by employing any vector including those of non-viral vectors such as cationic lipids remains unpredictable. For example, the state of the art exemplified by Verma *et al.* (Nature, Vol. 389, 18:239-242, September 1997) states that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph). In addition, Anderson, Nature, Vol. 392:25-30, 1998, summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several

years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

More importantly and even with applicant's exemplified DOPE/DOTAP liposomes, Filion (International J. of Pharmaceutics, 162:159-170, 1996, states:

[t]The use of cationic liposomes to target DNA to the gastrointestinal tract is inappropriate. Cationic DOPE/DOTAP liposomes are extremely toxic to CD1 mice following the administration of a single dose, provoking a profound and lethal hypothermia.

Complementary to our results, we have identified a range of adverse effects associated with the use of cationic lipids or cationic liposome (Table 2). This non-exhaustive list demonstrates very clearly that cationic liposomes must be used with caution for DNA (or drug) delivery. We believe that alternatives to cationic liposomes for DNA therapy should be considered in order to avoid these dose-limiting and often fatal adverse effect (page 169, column 1).

These results, in addition to the observation that cationic liposomes are extremely toxic following oral administration, indicate that DOPE/cationic lipid liposomes are not appropriate for DNA (or drug) delivery (abstract).

As such, there has been no evidentiary support from the as-filed application to show that on the basis of application's disclosure a skilled artisan would have been able to make and use the claimed cationic lipid/ligand/therapeutic liposomal complex in the context of any therapy other than cancer therapy and/or cancer gene therapy, nor is it apparent that *in vivo* transient gene expression provided by a cationic lipid used within the context of targeted gene therapy and/or systemic gene therapy can be used to treat any disease other than cancer. There is no evidence presented to show that the nexus from applicant's guidance and/or working examples to the subject matter as broadly claimed has been established.

Thus on basis of the *Wands* factors, it is not apparent how one skilled in the art determines, without undue experimentation, which of the disclosed DNA complexes generate a therapeutic effect in any and/or all gene therapy methods, nor is it apparent as to how one skilled in the art reasonably extrapolates from the disclosure of the as-filed specification to any and/or all *in vivo* delivery and/or expression methods wherein the only intended use of the methods is to generate a therapeutically intended effect, particularly given the lack of guidance and/or written support from the as-filed specification, the unpredictability of gene therapy, the lack of correlatble working examples, and/or the doubts expressed in the art of record.

Note that even while one of applicant's cationic lipid/biologically active molecule complex exhibits an inhibition effect on the growth of a tumor in a nude mouse, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

On this record, it is apparent that applicant's amended subject matter, without any proper written support and sufficient guidance from the as-filed specification, provides no more than a plan or invitation for those skill in the art to further unduly experiment with any cationic lipid/biologically active molecule complex other than those deemed enabling so as to provide any therapy effect in any animal.

Applicant's response and the Chang Declaration (all dated May 6, 2003) have been considered by the examiner but is only found persuasive with respect to the breadth of anti-tumor agent. The response and the Declaration do not overcome the remaining outstanding issues as set forth in the above rejection, particularly in view of the following reasons.

Both the response and Chang declaration indicate that the nude mouse model having a xenograft tumor is an art-recognized model in the field of cancer treatment, and that the NIC has a website which focuses an entire section on mouse model. The response is only found partially persuasive with respect to the use of nude mice for traditional anti tumor drugs, and the use immunocompetent mice for testing anti-cancer gene therapy vectors with the objective of correlating a therapeutically efficacy in ameliorating a tumor burden in cancer human patients. However, the outstanding issues as set forth in the above stated rejection with respect to the lack of reasonable correlation and/or predictability to practice the full breadth of the claimed invention are: 1/ The breadth of the claimed invention embraces any therapeutic DNA and/or any treatment effect in treating any mammal for cancer, which is not necessarily limited to a simple amelioration of a tumor in a cancer patient; 2/ all of the working examples including applicant's own published works employ a nude mouse model which is immunoincompetent, however, given that the effect of the immune system is one of many controlling and variable factors in determining the efficacy of the claimed liposomal vector employing any therapeutic DNA when used to treat a real world tumor bearing patient, let alone any patient at risk of having a cancer or any patient having a non-cancer disease. As such, the state of the prior art does not appear to dispute that the fact that a murine model is a useful model for experimentation of drugs and/or anti-tumor drugs other than cationic liposome

vectors encapsulating a therapeutic DNA. However, given the nature of the invention, the use of a nude (immunoincompetent) mouse in the working examples and/or applicant's cited references, and the doubts expressed in the art of record with respect to the complexities and/or *in vivo* barriers when cationic lipopsomes are used as cancer gene therapy vector, let alone any other gene therapy vector, specially when used within the context of systemic and targeted gene therapy, neither the as-filed application nor the cited references nor the Chang Declaration provides sufficient and substantial evidence to overcome the remaining outstanding issues. With respect to item 6 as indicated in the Chang Declaration, the office action does not dispute a reasonable enablement of the claimed invention within the context of employing anti-tumor agents and/or anti tumor therapeutic DNA in a method of ameliorating a tumor in a number of different tumor models, wherein encapsulating liposomes composed of DOTAP or DDAB/DOPE/folate or Transferrin/anti tumor DNA is employed. However, the fact that such data were demonstrated in the as-filed application, applicant's own published works and/or oral presentations (items 7 and 8) does not lend sufficient and substantial evidence to reasonably enable the full breadth of the claimed invention as presently claimed. Note also that in item 7 which indicates that two gene therapy clinical trials are being conducted is also not found persuasive because not only item 7 does not provide any evidence as to what are exactly the method and/or liposomal composition being used in the two clinical trial, item 7 also does not indicate as to which particular phase is being conducted for the non-specified clinical trials. Note that it is well-recognized in the art of cancer treatment that phase I clinical trial is directed to safety issues only. As such, until the details of the clinical trials are sufficiently submitted, the item 7 of the Chang Declaration is also not sufficient to overcome the rejection of the full breadth of the claimed invention.

On page 15 of the response, applicant asserts that sufficient guidance is provided by the as-filed specification, and that numerous references have been published to show the effectiveness of liposomal complexes comprising ligands other than the two exemplified in the application in targeting human tumor xenografts. Applicant's response together with the cited references, Xu (2001), Xu (2002) and Rait (2002),

have been considered fully and found partially persuasive, and as such, the enabling scope of the claimed invention as set forth in the above stated rejection has been modified to reflect applicant's reasonable enablement of claimed embodiments embraced by the full breadth of the claimed invention. However, neither the response nor applicant's post filing works and/or data are sufficient to overcome the remaining outstanding issues as set forth in the stated rejection.

On page 16, applicant asserts that the Lee reference is an old reference and therefore does not accurately reflect the state of the prior art, and that example 24 alone is sufficient to indicate that applicant 's invention works. However, not only the Lee reference was published in 1997 which fall within the effective filing date of the claimed invention, the facts and evidences set forth in the Lee reference do reflect the lack of reasonable predictability of the full scope of the claimed invention at the time of effective filing. Note that Example 24 is employed has been considered by the examiner and is already found reasonably correlatable to the enabling scope given in the above stated rejection. However, applicant's simple opinion or the working example 24, or the Xu reference (2002) does not provide sufficient and substantial evidence to demonstrate that any liposomal carrier and/or complexes other than those exemplified, *e.g.,* DOTAP or DDAB/DOPE/transferrin or folate/anti tumor DNA or beta-galactosidase or AS HER-2 ODN, can be reasonably practiced as a master cancer gene therapy vector for systemic administration of any anti tumor DNA, let alone for systemic administration of any other therapeutic DNA. In fact and to further rebut applicant's assertion that the state of the prior art at the time of filing of this as-filed application (1/2001) has advanced and overcome the doubts expressed in the Lee reference, the following references are cited to further rebut applicant's opinion:

Nishikawa (Human Gene Therapy 12, 8610870, May 2001) states (page 865, column 2):

In the case of cationic liposome-DNA complex, which shows minimal toxicity in animal and clinical studies after local administration, high levels of cytokines such as interferon y and tumor necrosis

factor α are observed after their intratracheal instillation or intravenous injection...The immune reaction against plasmid DNA is amplified by the use of cationic liposome. These cytokines not only cause toxicity in the treated animals but also inhibit transgene expression.

Nishikawa further concludes on column 2, page 866 that the successful clinical application of nonviral vectors even in 2001 remains to be resolved by basic research and will rely on a better understanding of the barriers to gene transfer and on the development of vectors that can overcome such barriers.

Notwithstanding the outstanding issues, which have not been overcome by substantial evidence provided by applicant's response or the Chang Declaration, applicant further asserts on page 18 that the phrases "optimism" and "will become more generally achievable" are evidences for enabling the full scope of the claimed invention. However, such phrases are further indicative of the lack of a reasonably predictability of the claimed invention at the time of the invention was made. The fact that there are hopes of a reasonable of predictability in the future is not considered sufficient evidence to overcome the remaining and outstanding issues for the claimed invention at the time of the invention was made.

Pages 18-23 of the response have been considered and are not found persuasive for enabling the full breadth of the claimed invention, particularly for the same reasons as set forth above. Note that the issue of targeting may be advanced by the use of a targeting ligand, however the issue does not overcome other unpredictable and variable factors such the nature and physiobiochemical properties of a particular liposome/DNA complex, the problem of *in vivo* transient gene expression, the problem of the immune reaction against *in vivo* gene expression, and other factors and/or doubts as set forth in the cited art of record. Note that applicant's response mostly refers to applicant's working examples and data shown in the cited references as the only evidence to indicate applicant's successful practice of the claimed invention. However, the claimed invention is broad and embraces an enormous number of

cationic liposomal vectors that are not necessarily limited to those employed in the working examples and cited references. As such and given the complexities and many variable factors existed for systemic administration of a liposomal vector, which complexities and factors are disclosed fully in many of the references cited in the stated rejection, it is not apparent how a skilled artisan, without any undue experimentation, practices the full breadth of the claimed invention, particularly on the basis of applicant's disclosure.

The 102(b) rejection by Wang has been withdrawn by the examiner because of the claim amendment.

The 102(e) and 103(a) rejection wherein the Cheng patent and reference are employed as the primary reference have been withdrawn by the examiner in view of the data provided in the Chang Declaration. However, the very same data are further indicative that the claimed invention at this stage of prosecution are properly limited to spherical or accentric structure based and encapsulating cationic liposome composed of DDAB or DOTAP/ligand/heper or neutral lipid/anti tumor agent. The newly submitted Chang Declaration clearly indicates that the DDAB/DOPE or DOTAP/DOPE liposomal carriers if made according to the guidance provided by the specification are spherical in shape and encapsulating DNA. The fact that the working example 1 provided in the Cheng reference is essentially the same as the guidance and/or claims in the as-filed application and yet does not produce the encapsulating cationic liposome having a spherical shape and a mean diameter of less than 100 nm is indicative of the lack of reasonable correlation between the exemplified cationic liposomal vectors and other liposomal vectors which are yet to be made but remain embraced by the full breadth of the claimed invention. As such, the totality of the art of record coupled with the nature of the invention and the breadth of the claimed invention do indicate that the claimed invention is not reasonably enabling in its full scope at the time the invention was made.

Note that even while one of applicant's cationic lipid/biologically active molecule complex exhibits

an inhibition effect on the growth of a tumor in a nude mouse, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER